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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,291	04/12/2001	Peter Krammer	4121-122	4237

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 10/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/834,291	Applicant(s) KRAMMER ET AL.	
	Examiner Daniel Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 12 April 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is a First Action on the Merits of the Application filed April 12, 2001, which is a 371 of PCT/DE99/03343, filed October 18, 1999, and claims priority to German Application DE 198 47 779.1, filed October 15, 1998. Claims 1-12, as originally filed, are pending in the application.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on October 15, 1998. It is noted, however, that applicant has not filed a certified copy of the DE 198 47 779.1 application as required by 35 U.S.C. 119(b).

In addition, a claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

Specification

The disclosure is objected to because of the following informalities: the specification and claims contain sequence that is not identified by SEQ ID No.

> "Where the description or claims of a patent application discuss a sequence that is set forth in the 'Sequence Listing' in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application" 37 C.F.R. 1.821.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a p53-binding region of a CD95 receptor DNA. The claims encompass a CD95 receptor DNA found in nature and are thus drawn to nonstatutory subject matter. Amending claim to indicate the hand of man in the invention (e.g. an isolated p53 binding region) would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are drawn to a p53 binding region of a CD95 cDNA wherein, in some embodiments, said p53 binding region can differ from the disclosed sequence by one or several base pairs. The claims are also directed to a vector comprising the p53 binding region and methods of using said p53 binding region. The disclosure provides that, "[t]he term 'p53' binding region' comprises any region of a CD95 receptor DNA to which a p53 may bind and *activate the CD95 receptor DNA, i.e. may induce it to transcribe*" (page 2, second full paragraph; emphasis added). Based on this definition, the claims are understood to be limited to a p53-binding region that exists within the regulatory region of a CD95 gene. Given their broadest reasonable interpretation, the claims encompass a genus of DNAs comprised within the regulatory region of a CD95 receptor DNA that retains p53-activated transcription. Therefore, the claims encompass the CD95 regulatory region from all species of organism wherein expression is regulated by p53. In addition, claims 2 and 3 encompass any DNA that binds p53, as the sequence may differ from the disclosed sequence by one or several base pairs. Please note that the limitation "several" has been interpreted to mean two or more.

The Revised Interim Guidelines state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)).

In the instant case, Applicant has disclosed the sequence of the human CD95 regulatory region and identified fragments thereof that retain p53 binding and transcriptional regulation. An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property, i.e. p53 binding, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *any* and *all* CD95 regulatory regions wherein expression is regulated by p53. Therefore, only the described nucleic acid sequences meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The disclosed invention provides p53 responsive DNA sequences which lie within the regulatory domain of the human CD95 gene. The claims encompass methods of treating any and all diseases wherein the p53 regulatory region of the CD95 receptor DNA is either activated or inhibited. With regard to treatment by inhibition of p53, the prior art does not provide any examples of such treatment either in humans or animals. In the case where guidance cannot be obtained from the prior art, the disclosure must provide sufficient guidance to enable the skilled artisan to practice the invention without undue experimentation. In the instant case, the

disclosure only provides that CD95 expression is regulated by p53 and that this information can be used in a method of treatment comprising inhibiting this regulation. No details are provided with respect to which conditions might be responsive to this therapy, what inhibitory agent should be used, or how the agent should be administered. Therefore, in order to practice the invention the skilled artisan would have to resolve each of these issues by empirical experimentation.

Regarding treatment wherein the p53 regulatory domain is inhibited, the specification (see especially Example 1 beginning on page 8) and relevant art (e.g. Owen-Schaub *et al.* (1995) *Mol. Cell. Biol.* 15:3032-3040) teach that some cancer chemotherapeutic agents induce expression of CD95 via a p53-dependent mechanism. There is also speculation in the art that the up-regulation of CD95 contributes to the therapeutic induction of apoptosis in cancer cells in response to chemotherapeutic agents. The art, however, also teaches that p53 mediated up-regulation of CD95 is not required for induction of apoptosis in many tumor cells. For example, Tolomeo *et al.* (1998) *Cell Death Diff.* 5:735-742 teach induction of apoptosis by a variety of chemotherapeutic agents in cell lines that do not express p53 (see especially Table 1 and the caption thereto and the second and third full paragraphs on page 740). Also, Ruiz-Ruiz *et al.* (1999) *Cell Death Diff.* (1999) 6:271-280 teach that blocking p53 activity did not alter the apoptotic response of a breast cancer cell line to doxorubicin (see especially Figure 6 and the caption thereto). These teachings raise questions as to the significance of the p53-induced up-regulation of CD95 in the apoptotic response to cancer chemotherapeutic agents. In considering the cited and similar findings, Friesen *et al.* (1999) *Leukemia* 13:1854-1858 teach, "[t]he discrepancy between different results may reflect differences in cell lines used, kinetics, cell

culture conditions, drug concentrations or effectiveness of blocking antibodies...Drug-induced apoptosis may also involve cell type-specific activation of parallel pathways such as death receptor pathways and mitochondrial pathways...Also, the CD95 system may not be a key effector in all instances and may contribute to chemosensitivity of tumor cells only in the early stages of drug treatment" (page 1856, column 2, second full paragraph). These teachings point out the unpredictability in inherent in the claimed method, as p53-induced up-regulation of CD95 has not been demonstrated to have an apoptotic effect or therapeutic potential in the absence of other cellular responses to chemotherapeutic drugs. Therefore, practicing the claimed invention as a therapeutic would require that the skilled artisan identify cells and conditions wherein the recited process would be an effective treatment. This would require significant empirical experimentation, thus placing an undue burden on one seeking to practice the invention.

Claims 6-9 provide for the use of a p53 binding region of a CD95 receptor, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 6-9 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Müller *et al.* (1998) 11:2033-2045.

Claims 1, 2, 4 and 5 are drawn to a p53-binding region of a CD95 receptor DNA. The claims have been examined according to the scope that meets the written description requirement of 35 USC § 112, first paragraph described above. Claim 2 limits the p53-binding region to a nucleic acid comprising the sequence of fig. 4 and/or fig. 5. The sequence limitations have been interpreted as follows: fig. 4 is equal to nucleotides 1-125 of SEQ ID NO:2 and fig. 5 is equal to nucleotides 44-63, 437-456 and 1266-1285 of SEQ ID NO:1. Claim 4 is drawn to a vector comprising the p53 binding region of claims 1-3 and claim 5 limits the vector comprising the p53-binding region of claim 4 to a construct selected from a group of defined constructs.

Müller *et al.* teach a p53-binding region from a CD95 receptor and sequence comprising nucleotides 1-125 of SEQ ID NO:2 (see especially the attached sequence alignment for Accession number AJ011034). Müller *et al.* also teach a vector comprising said p53-binding region from a CD95 receptor and specific constructs according to the instant application (compare Figures 10 and 11 of Müller *et al.* to Figures 5 and 6 of the instant application). The p53-binding region and vectors comprising said p53-binding region taught by Müller *et al.* are the same as those taught in the instant application.

Claim 10 is drawn to a process for influencing apoptosis, comprising the activation or inhibition of the p53 binding region of a CD95 receptor DNA according to any of claims 1-3. Müller *et al.* teach p53 mediated up-regulation of CD95 by tamoxifen and correlate an increased rate of apoptosis with this up-regulation (see especially Figure 7 and the caption thereto). The method of Müller *et al.* is the same as the method claimed in the instant application. The p53-binding region from a CD95 receptor, vector constructs comprising said p53-binding region and method of using said p53-binding region from a CD95 receptor can all be found within the teachings of Müller *et al.*, therefore the prior art anticipates the claims.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Rudert *et al.* (1995) *DNA Cell. Biol.* 14:931-937.

The limitations of the claims are described above. Rudert *et al.* teach a p53-binding region from a CD95 receptor DNA comprising nucleotides 44-63, 437-456 and 1266-1285 of SEQ ID NO:1 and a vector comprising said p53-binding region from a CD95 receptor DNA (see especially the Materials and Methods section beginning the first full paragraph of page 932 and continuing through the first paragraph of the second column on page 932; see also the attached alignment of SEQ ID NO:1 with Accession number X87625). Please note that, although Rudert *et al.* do not explicitly teach the p53-binding activity of the disclosed polynucleotide, the teachings anticipate the claims because the p53-binding activity is inherent to the disclosed polynucleotide. The limitations of the claims are therefore met by Rudert *et al.*

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Fulda *et al.* (1997) 57:3823-3829.

The limitations of claim 10 are recited above. Fulda *et al.* teach up-regulation of CD95 in response to a variety of cytotoxic drugs (see especially Figure 3 and the caption thereto) and that this up-regulation is likely p53-mediated (see especially the first paragraph of page 3826). Fulda *et al.* also demonstrate the influence of the up-regulation of CD95 on apoptosis by showing that antibodies against CD95 inhibit the apoptotic response to cytotoxic drugs (see especially Figure 4 and the caption thereto). The process taught by Fulda *et al.* is the same as the process taught in the instant application, therefore the limitations of the claim are met by Fulda *et al.*

Allowable Subject Matter

None of the claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
September 20, 2002

JAMES KETTER
PRIMARY EXAMINER